"PHYTOSOMES FOR BIOPHARMACEUTICAL OPTIMIZATION OF BIOLOGICALLY ACTIVE PLANT MOLECULES''

A SYNOPSIS

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By

Ms.Pande Shital Devidas

Mob. No. 7709988335

Email-shitalpande08@ gmail.com

Under the supervision of

Dr. S. C. Dhawale

Email- shashiprathmesh@gmail.com

Professor, School of Pharmacy,

SWAMI RAMANAND TEERTHMARATHWADA UNIVERSITY,
NANDED-431 606

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INTRODUCTION

"Phytosomes" are novel Phyto-phospholipid carriers for herbal drug delivery. The term "Phyto" means "Plant'', while "some" means "cell" like. Phytosomes are advanced microsphere or cell form of herbal product that are better absorbed, utilized to produce better result than those produced by conventional herbal extract[1]. As standardized extracts or phytoconstituent which are shows, poor bioavailability and limited their clinical utility. Prepare complexation with certain other clinically useful nutrients substantially improved the bioavailability of extracts. The nutrients so helpful for enhancing the absorption of other nutrients are the phospholipids. The enterocyte outer membrane has a lipid molecular bilayer that consists largely of Phosphotidylcholine [2]. Phospholipids is a principle molecular building block of cell membrane, making up the matrix into which fit a large variety of proteins that are enzymes, transport proteins, receptors, and other biological energy converters. In humans and other higher animals the phospholipids are also employed as natural digestive aids and as carriers for both fat-miscible and water miscible nutrients. Phosphotidylcholine are complex molecules that are used in all known life forms and responsible for formation of cell membrane [3].They derived from soybean, which is miscible both in the water phase & in oil, lipid phases excellently absorbed when taken orally [2].Phospholipids are small lipid molecule in which the glycerol is bonded only to two fatty acid instead of three as in triglycerides, and the remaining sites occupied by a phosphate group.

Phytosomes technology emerged in 1989 [6].Based on a histochemical observation that certain polyphenol had strong bonding affinity for phospholipids in their intact plant tissue. A group of Italian researchers focused on polyphenol preparations known to be poorly bioavailable when taken orally. These were typically mixtures of polyphenol extracted from single plant species, and their conversion into Phytosomes forms markedly increased their bioavailability [3]. It produce little cell because of that valuable component of herbal extract are protected from destruction by digestive secretion & gut bacteria [4].

Phytosomes are prepared by complexing the polyphenolic phytoconstituent in the ratio of 1:2 or 1:1 with Phosphotidylcholine [5].Phytosomes are obtained by reacting soya phospholipids with selected botanical derivatives in an aprotic solvent on the basis of their physical, chemical& spectroscopic characteristics. Their sizes vary between 50 nm to a few hundred μm. These complexes can be considered as novel entities [2].Phytosomes are not liposome's structurally [13].Phytosomes is unit of few molecules bonded together while liposome's as an aggregate of many phospholipids molecules but without specially bonding to them [4].Chemical analysis

indicates that in Phytosomes usually a the Tannins, flavonoids or Terpenoids components of these herbal extracts lend themselves quite well for the direct binding to Phosphotidylcholine. Bond is formed between these two molecules creating a hybrid molecule. Phytosomes are better able to transition from a hydrophilic environment into the lipid-friendly environment of the enterocyte cell membrane. These highly lipid miscible hybrid bond is better suited to merge in the lipid phase of the enterocytes outer cell membrane & finally reaching to blood circulation [5]. The Phytosomes process has been applied to many popular herbal extract including Ginkgo biloba, Grape seed, Milk thistle, Green tea, Curcumin, Herba Epimedii, Gallic acid and Ginseng etc [3].

ADVANTAGES OF PHYTOSOMES [3, 4]

1) It enhances the absorption of herbal constituent and hence the bioavailability.
2) Dose requirement has been reduced due to maximum absorption of chief Constituents.
3) Chemical bonds are formed between Phosphotidylcholine molecule & Phytoconstituent so the Phytosomes shows better stability profile.
4) Phytosomes produces a little cell where the valuable components of herbal extract are Protected from destruction by digestive secretion & gut bacteria.
5) Entrapment efficiency is high & more over predetermined because drug itself is in conjugation with lipids in forming vesicles.
6) Phosphotidylcholine used in formulating Phytosomes process besides acting as a carrier also act as Hepatoprotective which shows synergistic effect.

DIFFERENCE BETWEEN PHYTOSOMES AND LIPOSOMES: [6]

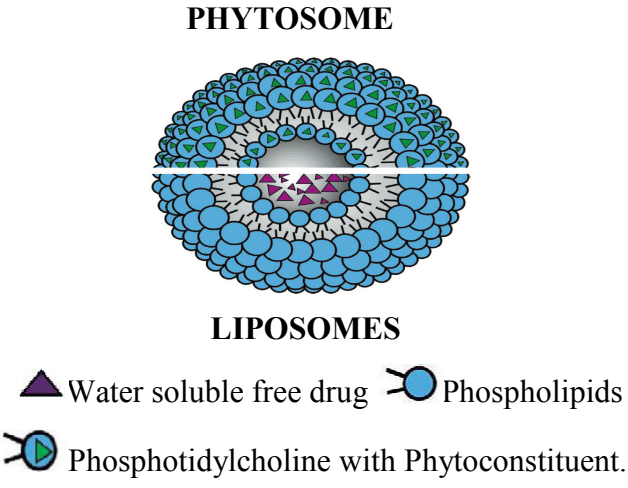


Figure1. Difference between Phytosomes and liposome

PHYTOSOME TECHNOLOGY

Phytosomes results from the reaction of as tachometric amount of the phospholipids (Phosphotidylcholine) with the standardized extract or polyphenolic constituents like simple flavonoids in a non polar solvent [2].Phosphatidylcholine is a bifunctional compound, the phosphatidyl moiety being lipophilic and the choline moiety being hydrophilic in nature. Specifically the choline head of the Phosphotidylcholine molecule binds to these compounds while the lipid soluble phosphatidyl portion comprising the body and tail which then envelopes the choline bound material. Hence, the phytoconstituent produce a lipid compatible molecular complex with phospholipids, also called as **Phyto-phospholipid complex**. Molecules are anchored through chemical bonds to the polar choline head of the phospholipids, as can be demonstrated by specific spectroscopic techniques Precise chemical analysis indicates the unit Phytosomes is usually a flavonoids, Terpenoids, Tannins molecule linked with at least one Phosphotidylcholine molecule. The result is a little micro sphere or cell is produced[5].

Figure 2: Organization of the Phytosomes molecular complex. Phytoconstituent (Lower right) is enveloped by a phospholipids molecule.

CHARACTERIZATION AND EVOLUTION OF PHYTOSOMES [5]

Phytosomes are characterized for physical attributes i.e. shape, size, its distribution percentage, drug release, drug capture, entrapped volume and chemical composition. There is different evaluation techniques used for Phytosomes. such as transmission electron microscopy (TEM) and scanning electron microscopy (SEM), Dynamic light scattering (DLS), Differential Scanning Colorimetry (DSC), IR spectroscopy.

Dementia is a chronic, progressive neurodegenerative disorder characterized by the decline of cognitive function. Alzheimer's disease (AD) is a progressive and complex neurodegenerative dementia and is a leading cause of death in elderly persons [6]. Disease, characterized by progressive decline in memory, language and it is associated with impairment of the basal forebrain cholinergic system, especially in the elderly [7]. Senile dementia of Alzheimer type (SDAT) has been shown to be associated with microtubule dysfunction and characterized by the appearance of specific cytoskeleton cellular abnormalities, including neurofibrillary bodies and senile plaques [8]. Of particular interest are the SDAT-associated changes in the cholinergic markers because of the possible association between these alterations and deficits in cognitive abilities [9]. It is now well established that free radical generation and subsequent oxidative damage occur prior to cytopathology and play a key role in the pathogenesis of AD [10]. Oxidative damage has been implicated as prime candidate mediating behavioral impairment and memory deficits in age-related neurodegenerative disorder [11].Most of the antialzheimer drugs used currently in clinical practice are cholinesterase inhibitor but are no longer available due to safety concerns [7].

Indian systems of medicine emphasize use of nutraceuticals, herbs or life style changes for controlling age related neurodegenerative disorders. it contains number of plants claimed to promote learning, memory and intelligence [12]for example Plants like Bacopa monaneria, Areca catechu, Celastrus paniculatus, Centella asiatica, Nardostachys jatamansi, Convolvulus pluricaulis, Commiphora mukul, Curcuma longa and Withania somnifera [13], has been investigated for their cognitive function on brain. These plants are grouped as Rejuvenators, means the drugs which counter the degenerative changes associated with ageing. Additionally some of these plants act specifically in augmenting the cognitive functions of the brain called as Nootropic agent [13]. Many natural products discovered from medicinal plants, or secondary metabolites such as terpenoids, phenolic acids, tannins, flavonoids, which exhibit significant antioxidant activity and shown promising health properties, Alzheimer's disease-like, suggestive of potential dietary strategies in dementia under experimental conditions [13], These drugs may help delay or prevent symptoms from becoming worse for a limited time and may help control some behavioral symptoms [15]. But due to low bioavailability of phytoconstituent needs to be enhanced for full exploitation of their therapeutic benefits in prevention and treatment of diseases [13]. Pharmacotherapy failure is the result of unfavorable absorption by biological membranes, unfavorable pharmacokinetic parameters instability of drugs, and toxicity to tissues.

The use of drugs in nanoplatforms or nanodevices results in the enhancement of their pharmacokinetics and pharmacodynamics, as well as they can to exhibit minimal toxicity [15].

INTERNATIONAL STATUS

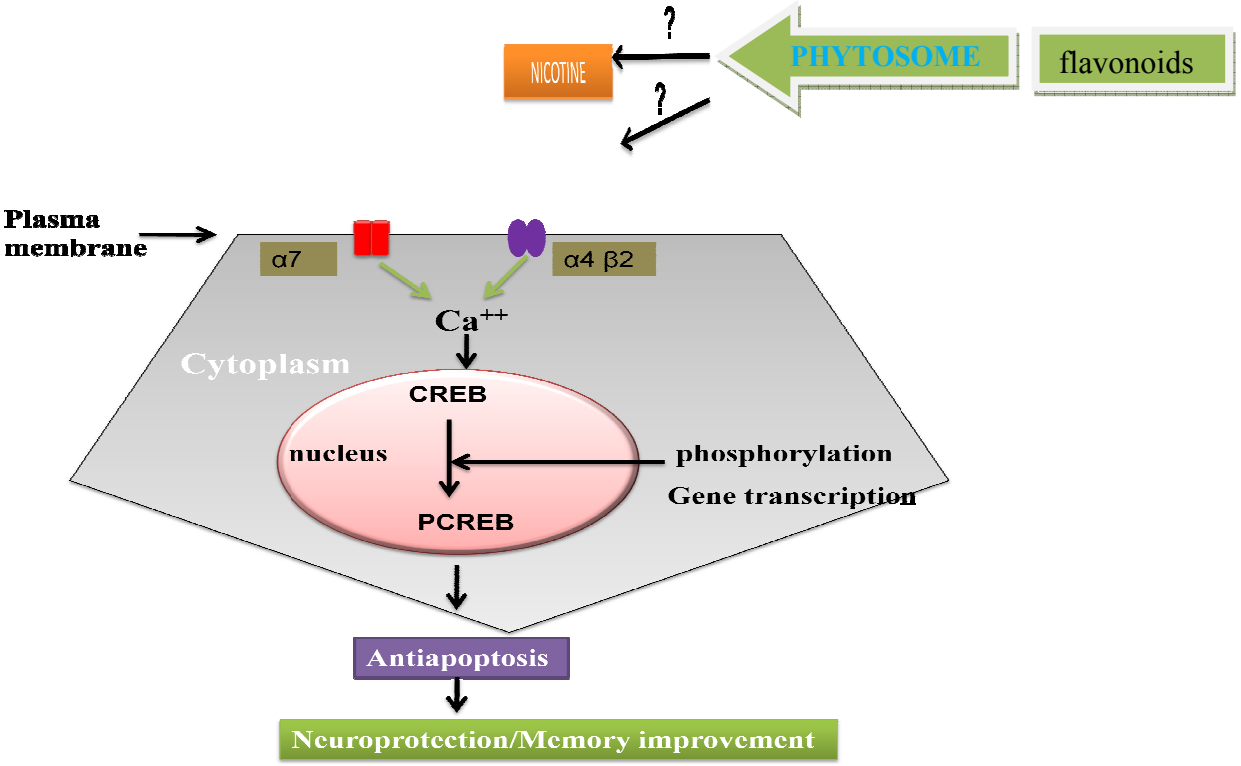
In the US, an estimated 5.2 million people of all ages have AD a number estimated to increase to7.7 million by 2030. This disease is the sixth leading cause of death in the US overall and the fifth leading cause of death for those aged 65 years and older. By 2050, the number of people aged 65 years and older with AD may nearly triple from 5 million to a projected 13.8 million unless medical breakthroughs are made to prevent, retard, or stop the disease progression. At the country level, ten countries are home to over a million people with dementia in 2015. More than 25 million people in the world are currently affected by dementia, most suffering from AD, with around 5 million new cases occurring every year[13].

NATIONAL STATUS

The prevalence of dementia in India is estimated to be around more than 4 million people have some form of dementia .India is world's 2nd largest in facing a terrible degenerative disease called Alzheimer's [18].People over the age of 60 are becoming victim of Alzheimer's, with women constituting 70 per cent of the total burden of the disorder [17].

HYPOTHESIS:

The living plants may be considered as a biosynthetic laboratory not only for the primary Metabolites like sugar, amino acid and fatty acids but also secondary metabolites such as alkaloids, glycosides, tannins, Terpenoids, flavonoids, phenolic acid, etc. These secondary metabolites may have prominent pharmacological and physiological actions due to topographic similarity but they are poorly absorbed either due to their large molecular size, multiple ring molecules that are too large to absorb by simple diffusion or due to their poor lipid solubility, severely limiting their ability to pass across the lipid rich biological membrane of erythrocytes of small intestine resulting poor bioavailability. The effectiveness of herbal product is depending on delivery & effective level of the active compound. To overcome these barriers the water soluble phytoconstituent molecule can be converted in to lipid compatible molecular complexes with the help of phospholipids to improved the bioavailability of extracts. On the basis of this it is hypothesized that Phytosomes prepare by using phytoconstituent of some plant and phospholipids will show better bioavailability with anti amnesic potential.



LITERATURE REVIEW

In current study stated that Cognitive dysfunction is a major health problem in the 21st century, neurodegenerative disorders, such as schizophrenia, depression, Alzheimer's Disease dementia, and Parkinsonism, can be severely functionally debilitating in nature. Phytochemicals from medicinal plants play a vital role in maintaining the brain's chemical balance by influencing the function of receptors for the major inhibitory neurotransmitters. neuroprotective active phytochemical substances like fatty acids, phenols, flavonoids, saponins, terpenes etc. Moreover, for a suitable neuroprotective agent, a very important property regards its ability to cross the blood-brain barrier (BBB), in order to reach the target sites of the CNS**. (G. Phani Kumar *et al*…2012)** Present works carried out with object that, the flavonoids as powerful antioxidant which play a key role in dementia. Investigated flavonoids incident cases of dementia were observed. It was concluded that the intake of antioxidant flavonoids is inversely related to the risk of incident dementia**. (D. Commenges *et al*…2002)** Flavonoids have shown promising health promoting effects in human cell culture, experimental animal and human clinical studies. They have shown antioxidant, anti-inflammatory effects as well as ability to modulate cell signaling and gene expression related disease development. Low bioavailability of flavonoids limits or even hinders their health effects. To improve their bioavailability in order to improve the efficacy of flavonoids needs to be enhanced for full exploitation of their therapeutic benefits in prevention and treatment of diseases. Therefore, continuing investigation is required to enhance the bioavailability and subsequent efficacy of certain flavonoids using consumer-friendly technologies **(Surangi H. *et al*…2013)**. Nanotechnology offers the potential for designing drug delivery systems with many properties. In the context of treating AD, nanosystems like Phytosomes, liposomes could efficiently carry and deliver drugs and other neuroprotective molecules to the brain. Oral, dermal, and intravenous routes can be used to administration of nanodevices to target to the brain passing by BBB to enhanced bioavailability, pharmacodynamic properties, and decreased adverse effects of these drugs to maximize pharmacotherapy in patients with AD. Nano-technology-based drug delivery systems that could lead to improved therapeutic outcomes with reduced costs **(Bruno Fonseca-Santos *et al*… 2015)**. Alzheimer's disease (AD) is the most prevalent form of dementia. Amyloid-$\beta_{25–35}$ a well-established neurotoxin is reported to be involved in the etiology of AD. Chrysin (CN) with its wide range of biological activities in terms of reversing the neuronal damage once induced is limited due to its compromised bioavailability. present investigation, CN loaded Solid lipid nanoparticles (SLNs) (CN-SLNs) was prepared and investigated its therapeutic role in alleviating A$\beta_{25–35}$ administered neuronal damage. Findings

from this study demonstrate that the therapeutic efficacy of CN could be attained at lower dose and also its oral bioavailability could be increased by encapsulating CN in SLNs. Thus the results suggest that CN-SLNs could be used as a potential therapeutic and a brain targeting strategy to combat the global burden of Alzheimer's disease. **(Aishwarya Vedagir *et al*… 2012).**

It was again investigated that orange juice rich in flavonoids showen anti-convulsant effects by both an inhibition of NMDA receptors at the glycine-binding site and an agonistic activity on benzodiazepine-binding site at GABAA receptors but due to less absorption of flavonoids there is need develop novel complementary therapy for the treatment of epilepsy in a context of a multitarget pharmacological strategy**.(Rita Citraro *et al*… 2016).**

Developed Gallic acid-Phospholipids complex in different ratio to improve the lipophilic properties of Gallic acid. The physicochemical properties of the, complex were analyzed by ultraviolet-visible spectrometry (UV), infrared spectrometry (IR) and differential scanning calorimetric (DSC) , solubility, dissolution, etc. & observed that complex was an effective scavenger of DPPH radicals and showed the strong antioxidant activity. (**Kumawat Radhey Shyam *et al*… 2012)**. Berberineis a potential natural alternative to other synthetic antidiabetic drugs. Due to poor gastrointestinal absorption and low oral bioavailability has limited its development for further clinical application Phytosomes loaded with berberine-phospholipid complex (P-BER) prepared by a rapid solvent evaporation method showed a nanoscale particle size an excellent drug entrapment efficiency (~85%).Compared to the orally administrated BER in previous pharmacokinetic studies, the oral bioavailability of the P-BER was significantly improved by 3 fold **(Fei Yu *et al*… 2016).**Bacopa phospholipids complex (BPC), a novel phytoformulation was prepared, characterized and evaluated for its possible enhancement of antiamnesic activity as compared to Bacopa extract (BE) in natural aging induced amnesic mice. Bacopa phospholipids complex has shown improved antiamnesic activity and higher serum concentration of bacopasides-I and bacopaside-II was observed for BPC in bioavailability studies as compared to Bacopa extract BPC maintained effective concentration of bacopasides for a longer period in rat serum**. (Prasanna Habbu *et al*… 2016).**

SIGNIFICANCE OF THE STUDY:

Natural phytoconstituent, often fail due to their poor solubility, lower bioavailability, and ineffective ability to cross the blood–brain barrier & due to the unfavorable pharmacokinetics and pharmacodynamics of drugs .Pharmacotherapy failure is the result of hydrophobicity, unfavorable absorption by biological membranes, unfavorable pharmacokinetic parameters (such as intense and plasma metabolism), instability of drugs, and toxicity to tissues. The use of drugs in nanoplatforms or phytosomal form results in the enhancement of their pharmacokinetics and pharmacodynamics, as well as they can to exhibit minimal toxicity. On the one hand, an essential aspect in nanomedicine development is the controlled release of drugs into disease sites. Without causing side effect on liver.

MATERIALS AND METHODS

1. Collection of standardized plant constituent

Preparation of Phytosome carried out by using standardized phytoconstituent flavonoids like Quarcetine, hesperidine, Naringenin, Apigenin, Catechin etc.

2. Extraction of Phospholipids

Isolation Phospholipid carried out by washing Ghee-residue with thrice its quantity of chilled acetone 3 times and discards the washings. The residue mix with equal quantity of ethyl alcohol at room temperature, warmed to 50^0-60^0C.cooled to room temperature the lipids extracted with equal amount of ethyl ether and petroleum-ether. The dried lipids dissolved in minimum quantity of ethyl ether. Precipitated with acetone at 5^0C.

3. Characterization of the isolated phospholipid using advanced analytical techniques

Isolated phospholipid characterization should be done by using advanced analytical techniques like UV Spectroscopy, FTIR, GCMS, HPLC and NMR etc.

4. Phytosomes preparation

Phytosomes prepare by using different ratio of standardized phytoconstituent and isolated phospholipid with the help of suitable method.

5. Characterization of Phytosomes

Prepared Phytosomes with optimized ratio selected for characterization, which is by

Transmission electron microscopy (TEM)

Scanning electron microscopy (SEM),

Differential Scanning Colorimetry (DSC)

IR spectroscopy.

Solubility study will be carried out by dissolution, Ex vivo technique

5. Pharmacokinetic study of optimized Phytosome

Pharmacokinetic study on optimized Phytosome will be carried out for assessment of bioavailability by using suitable animal model

6. **Evaluation of pharmacodynamic activity**

Pharmacodynamic evaluation of prepared Phytosomes will be carried out by using suitable animal model

Antialzheimer activity

Anticonvulsant activity

7. **Stereotoxic Study of Formulated Phytosome**

TENTATIVE DURATION OF WORK

Sr.N0.	WORK	PERIOD
1.	Literature survey	6 Months
2.	Procurement of standardized plant constituent	3 Months
3.	Procurement of Phospholipid	3 Months
4	Phytosomes preparation	3 Months
5.	Characterization of Phytosomes	3 Months
6.	Pharmacokinetic study of Phytosome formulation	6Months
7.	Evaluation of pharmacodynamic activity	9Months
8.	Other suggested work and compilation of data	3 Months
	Total duration of project	**36 Months**

RESEARCH OUTCOME

Most of the antialzheimer, anticonvulsant drugs used currently in clinical practice but are no longer available due to safety concerns. So there has been an intense search on various biological sources to develop a novel antialzheimer, anticonvulsant drug to combat this disease. patients who already got crippled with this disease, who are further burdened by drug-induced side effects, have now turned to seek help from the complementary and alternative medicine hoping for a better cure. Many natural products derived from plant such as terpenoids, phenolic acids, tannins, flavonoids, which exhibit significant antioxidant and other activities, have played an important role in treatment of convulsion and Alzheimer's disease. But as these compounds poorly absorbed either due to their large molecular size, multiple ring molecules that are too large to absorb by simple diffusion or due to their poor lipid solubility, severely limiting their ability to pass across the lipid rich biological membrane of erythrocytes of small intestine resulting poor bioavailability. Current study will investigates promising novel Phytosome from natural products which may have potent antialzheimer, anticonvulsant activity with improved pharmacokinetic and pharmacodynamic parameter.

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Research Student
Shital Pande
M. Pharm (Pharmaceutics)
School of Pharmacy
S R T M University, Nanded

Research Guide
Dr. S. C. Dhawale
Ph. D (Pharmacology)
Professor, School of Pharmacy
S R T M University, Nanded